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Office of Emergency and
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Washington DC 20460

Office of Research and Development
Office of Health and Environmental
Assessment
Environmental Criteria and
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Cincinnati OH 45268

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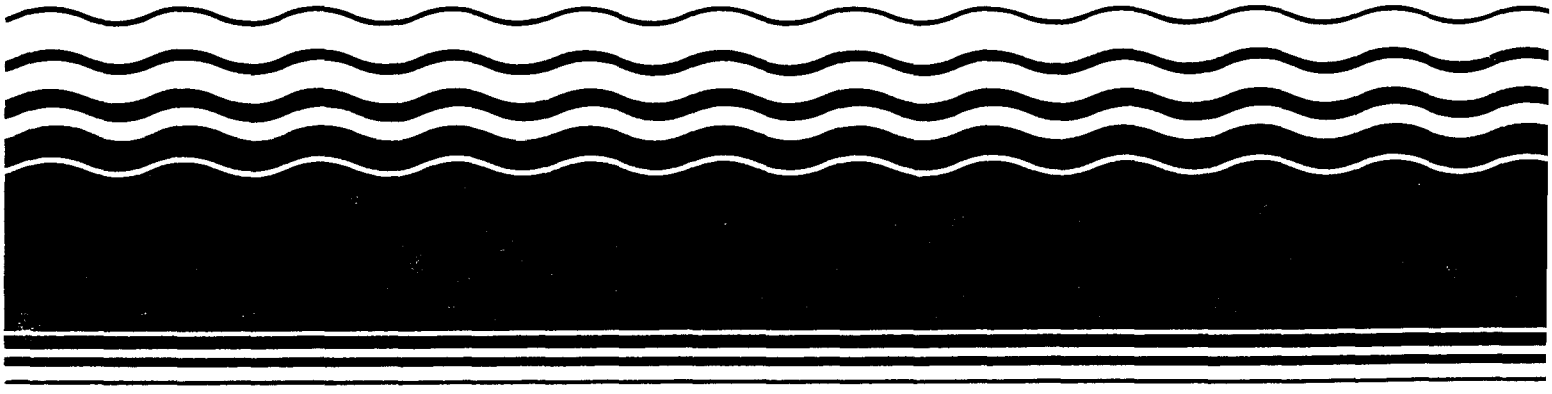
HEALTH EFFECTS ASSESSMENT FOR TETRACHLOROETHYLENE



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U.S. Environmental Protection Agency
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DISCLAIMER

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with tetrachloroethylene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Tetrachloroethylene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-073. NTIS PB 81-117830.

U.S. EPA. 1982. Hazard Profile for Tetrachloroethylene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-82-005F. NTIS PB 85-249704.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

A major issue of concern is the potential carcinogenicity of tetrachloroethylene. Human data are confounded by composite exposures. Results of in vitro mutagenicity bioassays are mixed. Only one animal bioassay employing oral exposure has been conducted. Results in rats were negative. In mice, tetrachloroethylene administration resulted in an increased incidence of hepatocellular carcinoma. Using this data, a q_1^* of 5.1×10^{-2} $(mg/kg/day)^{-1}$ was estimated.

The sole inhalation cancer bioassay available to date employed rats and failed to demonstrate an association between exposure to tetrachloroethylene and increased cancer incidence. U.S. EPA (1985) using appropiate pharmacokinetic conversions estimated a unit risk of 4.8×10^{-7} $(\mu g/m^3)^{-1}$ from the oral dose-response data.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
EEG	Electroencephalogram
LOAEL	Lowest-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of tetrachloroethylene (CAS No. 127-18-4) are given as follows:

Chemical class:	Halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	165.83
Vapor pressure:	17.8 mm Hg at 25°C (U.S. EPA, 1982)
Water solubility:	150 mg/ℓ at 25°C (Keil, 1979)
Octanol/water partition coefficient:	398 (U.S. EPA, 1982)
Soil mobility: (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%)	2.5 (Wilson et al., 1981)
Bioconcentration factor:	49 (in bluegill, Lepomis macrochirus) (U.S. EPA, 1980b)
	39 (in rainbow trout, Salmo gairdneri) (U.S. EPA, 1980b)
Half-life in air:	47 days (U.S. EPA, 1982)
Half-lives in water:	1-7 days, calculated from reaeration rate constant (Mabey et al., 1981)
	10-25 days (Wakeham et al., 1983)
	3-30 days (Zoeteman et al., 1980)

The half-life of tetrachloroethylene in soil could not be located in the literature searched. However, evaporation is expected to be the predominant loss mechanism from the soil surface (Wilson et al., 1981). The half-life for soil evaporation should be longer than its evaporation half-life from water (Wilson et al., 1981). In subsurface soil, no significant degradation of tetrachloroethylene from soil is expected (Wilson et al., 1983); therefore, leaching of this compound from soil to groundwater is likely to occur.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

Tetrachloroethylene is absorbed to some extent from the gastrointestinal tract (quantification and species not specified) (von Oettingen, 1964). Intestinal absorption by dogs is facilitated by fats and oils (Lamson et al., 1929).

2.2. INHALATION

The principal route by which tetrachloroethylene enters the human body is by pulmonary absorption in the alveolar air (U.S. EPA, 1985). Pulmonary absorption of tetrachloroethylene is rapid, and the amount of tetrachloroethylene absorbed at a given vapor concentration (for exposures of <8 hours) is directly related to the respiratory minute volume (Hake and Stewart, 1977). von Oettingen (1964) also reported that tetrachloroethylene is readily absorbed through the lungs (quantification and species not specified).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Pertinent data regarding the subchronic oral toxicity of tetrachloroethylene could not be located in the available literature.

3.1.2. Inhalation. The effects of subchronic inhalation exposure to tetrachloroethylene have been examined in rats, mice, rabbits, guinea pigs and monkeys. These effects are summarized in Table 3-1.

Carpenter (1937) exposed three groups of albino rats to tetrachloroethylene vapors at average concentration levels of 70, 230 or 470 ppm (equivalent to 475, 1560 or 3188 mg/m^3) for 8 hours/day, 5 days/week for 7 months. The control group consisted of 18 unexposed rats. After exposure and a 46-day rest period, rats exposed to 470 ppm tetrachloroethylene had cloudy and congested livers with swelling but no evidence of fatty degeneration or necrosis, increased renal secretion with cloudy swelling and desquamation of kidneys, and congested spleens with increased pigment. Following exposure to 230 ppm tetrachloroethylene and a 20-day rest period, treated rats at this level had similar but less severe pathologic changes as the highest exposure group. These changes included renal and splenic congestion and reduced hepatic glycogen storage. There was no evidence of pathologic changes in the liver, kidneys or spleen of animals exposed to 70 ppm tetrachloroethylene for 7 months. Upon microscopic examination of rats at each exposure level, Carpenter (1937) did not observe pathologic changes in the heart, brain, eyes or nerve tissue. Functional parameters (icteric index, Van den Bergh test for bilirubin, blood and urine analysis) were normal at all exposure levels. The fertility index (actual number of litters/possible number of litters) was increased for female rats receiving 150 exposures of 230 or 470 ppm tetrachloroethylene. A NOEL of 70 ppm

TABLE 3-1

Summary of the Animal Effects of Subchronic Inhalation Exposure to Tetrachloroethylene

Species	Dose (Concentration)	Exposure Period	Effects	Reference
Rats	15 ppm	4 hours/day for 5 months	EEG changes and protoplasmal swelling of cerebral cortical cells, some vacuolated cells and signs of karyolysis.	Dmitrieva, 1966
Rats	70, 230 or 470 ppm	8 hours/day, 5 days/week, for 150 exposures (7 months)	70 ppm: No pathological findings. 230 ppm: Similar, but less severe pathological findings as with higher dose; congestion and light granular swelling of kidneys. 470 ppm: Congested livers with cloudy swelling; no evidence of fatty degeneration or necrosis; evidence of kidney injury including increased secretion, cloudy swelling and desquamation; congestion of spleen.	Carpenter, 1937
Rats	100-400 ppm	7 hours/day, 5 days/week, for 6 months	No abnormal growth, organ function or histopathologic findings.	Rowe et al., 1952
Mice	15-74 ppm	5 hours/day for 3 months	Decreased electroconductance of muscle and "amplitude" of muscular contraction.	Dmitrieva, 1968

TABLE 3-1 (cont.)

Species	Dose (Concentration)	Exposure Period	Effects	Reference
Rabbits	15 ppm	3-4 hours/day for 7-11 months	Depressed agglutinin formation.	Mazza, 1972
Rabbits	15 ppm	3-4 hours/day for 7-11 months	Moderately increased urinary urobilinogen, pathomorphological changes in the parenchyma of liver and kidneys.	Navrotskii et al., 1971
Rabbits	100-400 ppm	7 hours/day, 5 days/week, for 6 months	No abnormal growth, organ function or histopathologic findings.	Rowe et al., 1952
Guinea pigs	0, 100, 200 or 400 ppm	7 hours/day, 5 days/week, for 132 or 169 exposures	100 ppm: Increased liver weights in females. 200 ppm: Increased liver weights with some fatty degeneration in both sexes; slight increase in hepatic lipid content; several small fat vacuoles in liver. 400 ppm: More pronounced liver changes than at 200 ppm; cirrhosis; increased liver weight; increase in neutral fat and esterified cholesterol in the liver; moderate central fatty degeneration.	Rowe et al., 1952
Monkeys	100-400 ppm	7 hours/day, 5 days/week, for 6 months	No abnormal growth, organ function or histopathologic findings.	Rowe et al., 1952

tetrachloroethylene for hepatic, renal and splenic pathologic changes in rats can be derived from this study.

Rowe et al. (1952) exposed rats, rabbits, guinea pigs and monkeys to tetrachloroethylene vapors at levels of 100-400 ppm for 7 hours/day, 5 days/week for ~6 months. No abnormal growth, organ function or histopathologic findings were seen at any exposure level among treated rats, rabbits or monkeys. Guinea pigs, however, were more susceptible to tetrachloroethylene, with adverse effects occurring at all exposure levels. Female guinea pigs exposed to tetrachloroethylene vapors at a level of 100 ppm had increased liver weights, while both sexes of guinea pigs exposed to 200 ppm had increased liver weights with some fatty degeneration, a slight increase in hepatic lipid content, and the presence of several small hepatic fat vacuoles. Guinea pigs exposed to the highest exposure level used in this study (400 ppm tetrachloroethylene) had more pronounced liver changes than at the 200 ppm exposure level, including cirrhosis, increased liver weight, increased hepatic neutral fat and esterified cholesterol, and moderate hepatic central fatty degeneration. A LOAEL of 100 ppm tetrachloroethylene for hepatic effects in guinea pigs can be derived from this study.

Four studies from the foreign literature (Dmitrieva, 1966, 1968; Mazza, 1972; Navrotskii et al., 1971) of subchronic inhalation exposure to tetrachloroethylene were summarized by U.S. EPA (1985). EEG changes and protoplasmal swelling of cerebral cortical cells, and the presence of some vacuolated cells and signs of karyolysis were seen in rats exposed to 15 ppm tetrachloroethylene vapors, 4 hours/day for 5 months (Dmitrieva, 1966). Mice exposed to 15-74 ppm tetrachloroethylene for 5 hours/day for 3 months had decreased electroconductance of muscle and "amplitude" of muscular contraction (Dmitrieva, 1968). Rabbits exposed to tetrachloroethylene

vapors at a level of 15 ppm for 3-4 hours/day for 7-11 months had depressed agglutinin formation (Mazza, 1972), and moderately increased urinary urobilinogen and pathomorphological changes in hepatic and renal parenchyma (Navrotskii et al., 1971). The lack of further details and dose-response data in these four studies from the Russian literature precludes their use for quantitative human risk assessment for inhalation exposure to tetrachloroethylene.

3.2. CHRONIC

3.2.1. Oral. The only source of information regarding chronic oral toxicity resulting from exposure to tetrachloroethylene is the National Cancer Institute (NCI, 1977) carcinogenicity bioassay with Osborne-Mendel rats and $B6C3F_1$ mice. Groups of 50 male and 50 female rats and mice received various levels of tetrachloroethylene in corn oil by gavage, 5 days/week for 78 weeks. TWA doses for this study were 450 and 550 mg/kg/day for male mice, 300 and 400 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats. Control groups consisted of 20 male and 20 female animals of each species that were either untreated or vehicle-treated. Toxic nephropathy was observed at all dose levels in both sexes of mice and rats. Therefore, the LOAEL for toxic nephropathy was 300 mg/kg/day for mice and 471 mg/kg/day for rats.

3.2.2. Inhalation. In a meeting abstract, Pegg et al. (1978) reported the results of a disposition study in Sprague-Dawley rats following inhalation exposure to tetrachloroethylene at a level of 4 g/m^3 (600 ppm) for 6 hours/day, 5 days/week for 12 months. Unspecified reversible liver damage was observed in the treated rats.

Human health effects as a result of chronic inhalation exposure to various concentrations of tetrachloroethylene include respiratory tract

irritation, nausea, headache, sleeplessness, abdominal pains and constipation (Chmielewski et al., 1976; Coler and Rossmiller, 1953; Stewart et al., 1970; von Oettingen, 1964). Liver cirrhosis, hepatitis and nephritis have also been reported (Stewart, 1969). Side effects from the therapeutic use of tetrachloroethylene as an antihelmintic agent also have been reported (von Oettingen, 1964). Lack of dose quantification and a dose-response relationship precludes the use of these human data for quantitative risk assessment for inhalation exposure to tetrachloroethylene.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding the teratogenicity of tetrachloroethylene following oral administration could not be located in the available literature.

3.3.2. Inhalation. Schwetz et al. (1975) exposed 17 pregnant Sprague-Dawley rats and 17 pregnant Swiss-Webster mice to tetrachloroethylene by inhalation at a level of 300 ppm (2035 mg/m^3) for 7 hours/day on days 6-15 of gestation. Caesarean sections were done on day 18 (mice) or 21 (rats). Maternal rats had a statistically significant reduction in mean body weight, while maternal mice had increased mean relative liver weight. The fetal body weight of mice was significantly depressed. A significantly increased number of rat fetuses were resorbed. For mice, the incidences of subcutaneous edema, delayed ossification of skull bones, and split sternebrae were significantly increased, compared with those incidences in control mice.

3.4. TOXICANT INTERACTIONS

Compounds that alter the functional activity of microsomal enzyme systems may affect the toxicity of tetrachloroethylene because it is metabolized by mixed function oxidases (U.S. EPA, 1980b). Phenobarbital pretreatment, however, did not modify the acute hepatotoxicity of tetrachloro-

ethylene (Cornish et al., 1973, 1977). Induction of mixed function oxidases by pretreatment with Aroclor 1254 resulted in altered tetrachloroethylene acute toxicity, manifested by vacuolization of rough endoplasmic reticulum and increased serum glutamate oxalacetate transaminase activity (Moslen et al., 1977; Reynolds and Moslen, 1977).

Tetrachloroethylene has been associated with intolerance to alcohol, probably because both tetrachloroethylene and alcohol are CNS depressants (Gold, 1969). Synergistic effects, identified by lethality as the endpoint, of mixtures of tetrachloroethylene and benzene following intubation to rats have been reported (Withey and Hall, 1975).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity of orally administered tetrachloroethylene to humans could not be located in the available literature.

4.1.2. Inhalation. In a study of 330 deceased laundry and dry-cleaning workers with a history of exposure to tetrachloroethylene, carbon tetrachloride and trichloroethylene, Blair et al. (1979) observed an excess of lung, cervical and skin cancers and a slight excess of leukemias and liver cancers. Blair et al. (1978) reported five cases of chronic lymphocytic leukemia among a family that operated a dry-cleaning business.

4.2. BIOASSAYS

4.2.1. Oral. The only source of carcinogenicity data from oral exposure to tetrachloroethylene is the NCI (1977) carcinogenicity bioassay with Osborne-Mendel rats and $B6C3F_1$ mice. Groups of 50 male and 50 female rats and mice received various levels of tetrachloroethylene in corn oil by gavage, 5 days/week, for 78 weeks. TWA doses for this study were 536 and 1072 mg/kg/day for male mice, 386 and 772 mg/kg/day for female mice, 471 and 941 mg/kg/day for male rats, and 474 and 949 mg/kg/day for female rats. Control groups consisted of 20 male and 20 female animals of each species that were either untreated or vehicle-treated. All surviving mice were killed at 90 weeks and all surviving rats at 110 weeks. Decreased survival rates were observed for both species. No increases in tumor incidences were observed for treated rats. Mice, however, were observed to have highly significant increases in hepatocellular carcinomas. The incidences of this tumor type in mice were 2/17 untreated control males, 2/20 vehicle control males, 32/49 low-dose males, and 27/48 high-dose males; and 2/20 untreated

control females, 0/20 vehicle control females, 19/48 low-dose females, and 19/48 high-dose females. Metastases were reported for one untreated control male, three low-dose males, one low-dose female and one high-dose female.

4.2.2. Inhalation. Rampy et al. (1977) exposed groups of 96 male and 96 female Sprague-Dawley rats to tetrachloroethylene vapors at levels of 2 or 4 g/m^3 (300 or 600 ppm, respectively) for 6 hours/day, 5 days/week for 12 months. There was no statistically significant difference in any tumor incidence between treated and control animals.

4.2.3. Selected Pharmacokinetics Relevant to Interspecies Extrapolation. U.S. EPA (1985) evaluated the pharmacokinetics of tetrachloroethylene relevant to interspecies dose response extrapolation. The material in this section is excerpted from U.S. EPA (1985). It is generally recognized that the carcinogenicity of the chlorinated ethylenes relates to their metabolic conversion to biologically reactive intermediates. The metabolism of tetrachloroethylene has been investigated in the mouse, rat and man. In general, the end metabolites have been poorly characterized across these species, and there is no experimental evidence which indicates qualitative differences in metabolic pathways.

Pharmacokinetic/metabolic evaluations following oral exposure considered most relevant to species extrapolation include Pegg et al. (1979), Schumann et al. (1980), and Buben and O'Flaherty (1985).

Pegg et al (1979) and Schumann et al. (1980) administered ^{14}C tetrachloroethylene in corn oil to Sprague-Dawley rats and B6C3F$_1$ mice as single intragastric doses of 1 or 500 mg/kg. ^{14}C radioactivity was measured in exhaled breath, urine, feces and carcass for 72 hours following dosing. In addition, pulmonary excretion of parent compound was monitored. The results of these investigations as presented by U.S. EPA (1985) are shown in Table 4-1.

TABLE 4-1

Disposition of ^{14}C-PCE Radioactivity for 72 Hours After Single Oral Doses to Sprague-Dawley Rats and $B6C3F_1$ Mice[a]

	Rats (average of 3)[b]		Mice (average of 3)
	1 mg/kg (0.25 mg/kg/animal)	500 mg/kg (125 mg/animal)	500 mg/kg (12.25 mg/animal)
	mg-eq per animal	mg-eq per animal	mg-eq per animal
Expired unchanged	0.174 (71%)	110.67 (90%)	8.90 (83%)
Metabolized			
$^{14}CO_2$	0.007	0.57	0.14
Urine	0.040	5.72	1.53
Feces	0.015	4.82	0.13
Carcass	0.008	1.41	0.05
	0.070 (29%)	12.52 (10%)	1.85 (17%)
Total	0.244	123.19	10.75

[a]Source: U.S. EPA, 1985

[b]Based on average experimental animal weight (grams): 250, rat; 24.5, mouse.

For rats, 29% and 10% of the 1 and 500 mg/kg doses, respectively was metabolized, indicating metabolism which is both limited and saturable. In mice given 500 mg/kg 17% of the dose was metabolized. The ratio of the metabolized dose in rats:mice calculated by U.S. EPA (1985) is 6.77. U.S. EPA (1985) concluded that this relationship indicated that the comparative metabolism of tetrachloroethylene was more consistent with a surface area than a body weight proportionality.

Buben and O'Flaherty (1985) examined tetrachloroethylene metabolism in male mice dosed 5 days/week for 6 weeks by gavage using a corn oil vehicle. They found that metabolism was both saturable and dose-dependent. Metabolism was evaluated based on the level of urinary trichloroacetic acid (TCA). U.S. EPA (1985) judged that urinary TCA is expected to represent 70-80% of total tetrachloroethylene metabolized. The data from this study are shown in Figure 4-1. Comparison of the amount metabolized from the Schumann et al. (1980) and Pegg et al. (1979) studies where mice were given 500 mg/kg to the amount metabolized for a 500 mg/kg dose based on Figure 4-1 indicates good agreement between the two studies. The molar equivalent metabolized dose from Figure 1 (367 μmoles) represents 80% of the molar equivalent metabolized dose (455 μmoles) from Schumann et al. (1980) and Pegg et al. (1979).

4.3. OTHER RELEVANT DATA

Tetrachloroethylene elicited a positive response in both the Salmonella typhimurium reverse mutation assay and the host-mediated assay in mice, using S. typhimurium (Cerna and Kypenova, 1977). Tetrachloroethylene was negative in forward mutation assays with Escherichia coli (Greim et al., 1975) and failed to induce chromosomal aberrations in bone marrow cells of mice that had received 1 or 5 daily intraperitoneal injections of the compound (Cerna and Kypenova, 1977).

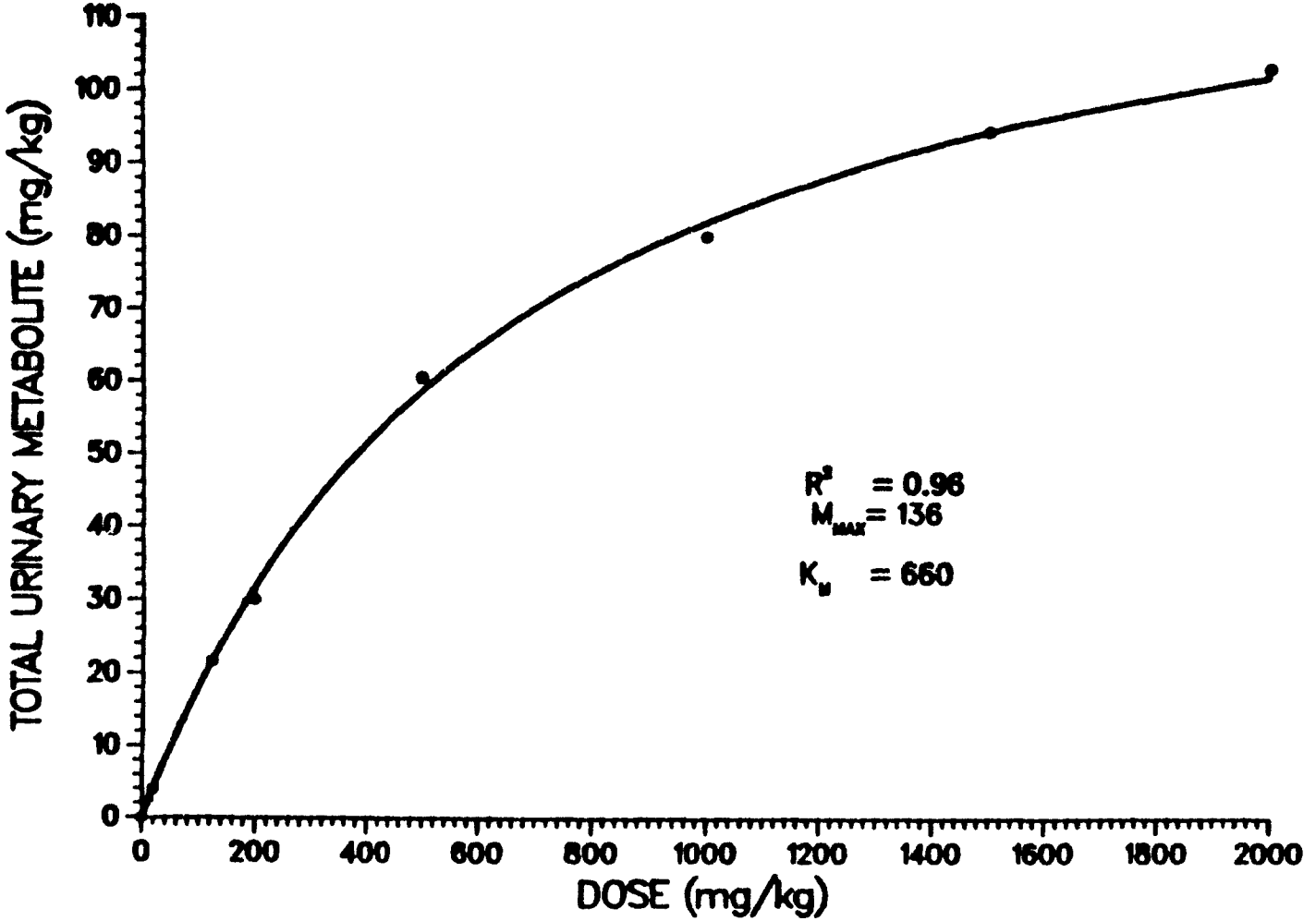

FIGURE 4-1

Relationship Between the PCE Dose and the Amount of Total Urinary Metabolite Excreted per Day by Mice in Each Group

Source: U.S. EPA, 1985

4.4. WEIGHT OF EVIDENCE

IARC (1979) concluded that there was limited evidence that tetrachloroethylene is carcinogenic in mice, based on the increased incidence of hepatocellular carcinomas in both sexes of mice following oral administration of tetrachloroethylene (NCI, 1977). Human carcinogenicity data, consisting of a proportionate mortality study of 330 former laundry workers, was considered to be inadequate for assessing human cancer risk associated with exposure to tetrachloroethylene (IARC, 1982). Likewise, the evidence for tetrachloroethylene activity in short-term tests was considered inadequate (IARC, 1982). Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating the overall weight of evidence of carcinogenicity to humans (Federal Register, 1984), tetrachloroethylene is most appropriately designated a Group C - Possible Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

ACGIH (1983) has recommended a TWA-TLV of 50 ppm and a STEL of 200 ppm. OSHA has established a permissible exposure level (8-hour TWA) of 100 ppm (Code of Federal Regulations, 1981).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Tetrachloroethylene is a chemical demonstrated to be carcinogenic in animals, and for which data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to calculate an AIS for this chemical.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Tetrachloroethylene is a chemical demonstrated to be carcinogenic in animals, and for which data are sufficient for estimation of carcinogenic potency. It is inappropriate, therefore, to calculate an AIC for this chemical.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. U.S. EPA (1985) based on the data of Buben and O'Flaherty (1985) estimated the quantity of metabolites contributing to the carcinogenic response for the NCI (1977) study in $B6C3F_1$ mice as follows:

	NCI Gavage Dose (mg/kg/day)	Urinary Metabolites (mg TCA/kg/day)	% Increase with Dose
Males	536	60.95	
	1072	84.18	38
Females	386	50.19	
	772	73.32	46

Potency estimates expressed in terms of both metabolized and administered dose are shown in Table 6-1. Potency in terms of administered dose (A) was calculated from potency in terms of metabolized dose using the relationship M=0.2A. This relationship was estimated by U.S. EPA (1985)

TABLE 6-1

Dose Response Data and Potency (Slope) Estimates

	Animal Time-weighted Average Metabolized Dose (mg/kg/day)[a]	Tumor Incidence[b]	Human Potency Estimate in Terms of Metabolized Dose $(mg/kg/day)^{-1}$	Human Potency Estimate in Terms of Administered Dose[c] $(mg/kg/day)^{-1}$
Males	0	2/20		
	37.73	32/48		
	52.11	27/45	3.4×10^{-1}	6.8×10^{-2}
Females	0	0/20		
	31.07	19/48		
	45.39	19/45	2.5×10^{-2}	5.1×10^{-2}

[a]Calculated from metabolized dose data shown in Table 4-1 by multiplying by 78 weeks/90 weeks and 5 days/7 days

[b]The denominators are the number of animals that survived at the time the first hepatocellular carcinoma occurred in each study

[c]Human potency estimates were calculated from animal potency estimates by multiplying by $(weight_{human}/weight_{animal})^{1/3}$

based on the data of Buben and O'Flaherty (1985). For comparative purposes, potency was also calculated using metabolized dose estimated from the data of Schumann et al. (1980). There was good agreement between the estimates generated by the two methods. U.S. EPA (1985) recommended that the potency estimate calculated from tumor incidence in female mice, 5.1×10^{-2} $(mg/kg/day)^{-1}$, be used to represent the potency of tetrachloroethylene because the dose-response data for female mice were "more reliable" than for male mice.

6.3.2. Inhalation. In the only inhalation cancer assay available to date, Rampy et al. (1977) did not find any statistically significant difference in any tumor incidence between control rats and those exposed to tetrachloroethylene vapors at levels of 2 or 4 g/m^3 (300 or 600 ppm, respectively), 6 hours/day, 5 days/week, for 12 months. U.S. EPA (1985) calculated unit risks for inhalation exposure using a variety of pharmacokinetic approaches for route extrapolation. The unit risk of 4.8×10^{-7} $(\mu g/m^3)^{-1}$ was recommended for use as the representative estimate. This estimate was based upon the relationship between exposure concentration and tetrachloroethylene metabolites in urine from the data of Bolanowska and Golacka (1972). In the study, five subjects were exposed to 390,000 $\mu g/m^3$ tetrachloroethylene for 6 hours. Metabolites in the urine were monitored for 20 hours. The total amount of metabolites was estimated to be 13 mg (U.S. EPA, 1985). The amount of metabolites up to 20 hours was taken directly from the experimental data. The remainder of the area, under the curve, 20 hours to infinity, was estimated as:

$$C \times T_{1/2} / 0.693$$

where:

C = concentration of metabolites at the last sampling time
$t_{1/2}$ = assumed to be 100 hours

Assuming that the amount metabolized is linearly related to the air concentration and the duration of exposure, the amount metabolized associated with 1 $\mu g/m^3$ of tetrachloroethylene in air is:

$$(13 \text{ mg}/39{,}000 \text{ mg}/m^3) \times (24 \text{ hours}/6 \text{ hours}) = 1.33 \times 10^{-4} \text{ mg/day}$$

or

$$1.9 \times 10^{-6} \text{ mg/kg/day}$$

The cancer risk associated with exposure to 1 $\mu g/m^3$ tetrachloroethylene is:

$$2.5 \times 10^{-1} \text{ (mg/kg/day)}^{-1} \times 1.9 \times 10^{-6} \text{ mg/kg/day} = 4.8 \times 10^{-7} \text{ } (\mu g/m^3)^{-1}$$

Assuming a human breathes 20 m^3 of air in 24 hours and weighs 70 kg, this unit risk may be expressed as 1.68×10^{-3} $(mg/kg/day)^{-1}$.

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APPENDIX

Summary Table for Tetrachloroethylene

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1*	Reference
Inhalation	mice	536-1072 mg/kg/day	hepatocellular carcinoma	1.68×10^{-3}	NCI, 1977; U.S. EPA, 1985
Oral	mice	536-1072 mg/kg/day	hepatocellular carcinoma	5.1×10^{-2} $(mg/kg/day)^{-1}$	NCI, 1977; U.S. EPA, 1985